INPLASY PROTOCOL

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Support: **Zhuji Affiliated Hospital.**

Review Stage at time of this submission: **Formal screening of search results against eligibility criteria.**

Conflicts of interest:
None.

A comparison of the efficacy and safety of combined aclidinium bromide and formoterol fumarate in the treatment of chronic obstructive pulmonary disease

Lu, H[1]; Chen, YT[2]; Chen, HJ[3]; Chen, PF[4].

Review question / Objective: **Patient or population: people with COPD; Intervention: FDC aclidinium/formoterol; Comparison: aclidinium; Outcomes: i) exacerbations (number of patients experiencing one or more exacerbations), ii) St George's Respiratory Questionnaire (SGRQ) score change from the baseline, iii) transitional dysponea index (TDI) score change from the baseline, iv) trough forced expiratory volume in one second (FEV1) change from the baseline, and v) adverse events (not serious adverse events, serious adverse events, and total adverse events).**
Condition being studied: **Clinical and experimental studies have confirmed that combined aclidinium bromide and formoterol fumarate can reduce the frequency of acute exacerbations, improve the quality of life, and reduce the severity of inflammation. However, there is still a lack of systematic review to analyze the clinical evidence of combined aclidinium bromide and formoterol fumarate in the treatment of COPD. Therefore, a comprehensive review is urgently needed to support the effectiveness and safety of combined aclidinium bromide and formoterol fumarate on patients with COPD. In this work, we will summarize the existing evidence and evaluate the efficacy and safety of combined aclidinium bromide and formoterol fumarate for COPD.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 July 2020 and was last updated on 15 July 2020 (registration number INPLASY202070063).

INTRODUCTION

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METHODS

Participant or population: People with COPD.

Intervention: FDC aclidinium/formoterol.

Comparator: Aclidinium.

Study designs to be included: Randomized controlled trial

Eligibility criteria: Types of studies. Only randomized controlled trials (RCTs) of combined aclidinium bromide and formoterol fumarate for the treatment of COPD will be included. However, we will exclude any other studies, such as animal studies, case report, case series, review, comments, nonclinical trials, uncontrolled trials, and quasi-RCTs. 2.2.2. Types of participants. Any patient who was diagnosed as COPD will be included irrespective of sex, age, and severity of COPD. 2.2.3. Types of interventions. In the experimental group, all patients who received combined aclidinium bromide and formoterol fumarate treatment will be included. In the control group, all patients received any management without restrictions. However, if we identified any study that involved any forms of combined aclidinium bromide and formoterol fumarate as their comparator, we will exclude it. 2.2.4. Type of outcome measurements. Primary outcome is lung function, which was measured by forced vital capacity or forced expiratory volume in 1 second or other.

Information sources: Electronic searches will be performed systematically and comprehensively for relevant studies in PubMed, MEDLINE, EMBASE, Cochrane Library Central Register of Controlled Trials, WANGFANG, and CNKI. All these databases will be conducted from inception to the present regardless of their language and publication time. Similar search strategies will be adapted and applied to other electronic databases.

Main outcome(s): Primary outcome is lung function, which was measured by forced vital capacity or forced expiratory volume in 1 second or other relevant tools.

Quality assessment / Risk of bias analysis: The methodological quality of the RCTs will be evaluated by 2 independent reviewers (Huang Yitong and Chen Peifeng) using the Cochrane Collaborations tool. The risk of bias of a trial is assessed through 6 items, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. These items will be classified into 3 levels: "Low risk", "High risk" or "Unclear risk". Disagreements will be discussed and arbitrated by all reviewers.

Strategy of data synthesis: We used a random-eKects model and performed a sensitivity analysis using a fixed-eKect model. We applied a fixed-eKect model if the I2 statistic showed homogeneous results, and a random-eKects model for data synthesis when there was significant heterogeneity (I2 greater than 50%) that

could not be explained by subgroup analyses.

Subgroup analysis: We planned to carry out the following subgroup analyses. i) Dose of LABAs (e.g. formoterol 6 µg, formoterol 12 µg). We also planned to use the following outcomes in subgroup analyses. i) Exacerbations requiring a short course of an oral steroid or antibiotic, or both. ii) Quality of life. iii) adverse events.

Sensibility analysis: We planned to carry out the following sensitivity analyses. i) Repeating the meta-analysis after exclusion of trials with high risk of bias or unclear methodological data. ii) Performing the meta-analysis by using both a random-effects model and a fixed-effect model.

Country(ies) involved: China.

Keywords: Aclidinium, formoterol, Adverse events, Exacerbations, SGRQ, Trough FEV1, TDI.

Contributions of each author:
Author 1 - Hong Lu - Data curation, formal analysis, methodology, and writing.
Author 2 - Yi-Tong Chen - Software, supervision, and wirting.
Author 3 - He-Jiang Chen - Data curation, formal analysis, software, and visualization.
Author 4 - Pei-Feng Chen - Resources, investigation, and data curation.